Electrical Stimulation Devices (ESDs) for Aversive Conditioning

Neurological Devices Panel
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FDA Introduction

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FDA Review Team

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- Lawrence Park, M.D. (Psychiatrist)
- Michelle Roth-Cline, M.D., Ph.D. (Pediatric Ethicist, OPT)

Presentation Outline

Aversive Conditioning Devices Regulatory History -

- **Introduction:** Kristen Bowsher, Ph.D.
- **FDA Standard for Banning**: Vincent Amatrudo, J.D.
- **Regulatory History and Device Description**:

  Kristen Bowsher, Ph.D.

FDA Clinical and Scientific Presentation -

- **Clinical Background Information Regarding Self-Injurious Behavior (SIB) and Aggressive Behavior**: Peter Como, Ph.D.
- **Benefits and Risks of ESDs for Aversive Conditioning:**

  Lawrence Park, M.D.
- **Ethical Considerations with Particular Focus on Issues Related to Clinical Studies:** Michelle Roth-Cline, M.D., Ph.D.
- **Summary:** Kristen Bowsher, Ph.D.

Purpose of Meeting

The FDA is concerned that ESDs for aversive conditioning intended to deliver a noxious electrical stimulus to modify undesirable behavioral characteristics in patients who exhibit SIB and aggressive behavior may present a substantial and unreasonable risk of illness or injury. Therefore, FDA is considering banning these devices under 516 of the FD&C Act.

Purpose of Meeting

To seek scientific and clinical expert opinion on:

- Risks and benefits associated with other treatment options for this population. (Panel Question 1)
- Risks and benefits of ESDs for aversive conditioning to modify undesirable behavioral characteristics in patients who exhibit SIB and aggressive behavior. (Panel Questions 2)
- Whether ESDs for aversive conditioning present a substantial and unreasonable risk of illness or injury. (Panel Question 3)
- Potential approaches to risk mitigation. (Panel Question 4)

Purpose of Meeting

To seek scientific and clinical expert opinion on:

- The risks and benefits of applying the ban to devices currently in use by patients. (Panel Question 5)
- Whether a clinical trial could be conducted to evaluate ESDs for aversive conditioning for the treatment of SIB and aggressive behavior. (Panel Question 6)

FDA Standard for Banning

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Legal Background: Banning Under the FD&C Act

- FDA Standard for Banning
- Evidence and Labeling Requirements
- Applicability of the Ban to Devices in Distribution and Use

FDA Standard for Banning

- Under the statute, a medical device for human use may be banned if it presents "substantial deception or an unreasonable and substantial risk of illness or injury" (FD&C Act 516)
  - » Bans must be imposed by regulation
    - Notice-and-comment rulemaking (typically a proposed rule → comments → a final rule)
  - » FDA is focused on the "unreasonable and substantial risk of illness or injury" prong

FDA Standard for Banning

- In evaluating whether a risk of illness or injury is "unreasonable and substantial," the following considerations apply:
  - » Is the risk important, material, or significant in relation to the device's benefit to the public health? (21 CFR 895.21(a))
  - » Is the risk reasonable in light of the state of the art? (44 FR 29215)
- Actual proof of illness or injury is not required (44 FR 29215)

Evidence and Labeling Requirements

- A banning determination must be based on “all available data and information,” which can include data obtained under other statutory provisions, information supplied by manufacturers, and voluntarily submitted information
- FDA may ban a device if it determines that the risk of illness or injury cannot be corrected or eliminated by labeling (21 CFR 895.20)

Applicability of the Ban to Devices in Distribution and Use

- A ban may apply to medical devices:
  - » Not yet in commercial distribution
  - » In commercial distribution, excluding those already sold to the ultimate user
  - » In commercial distribution and sold to the ultimate user
- The final banning regulation must specify whether the ban applies to devices already in commercial distribution and/or sold to the ultimate user (21 CFR 895.21(f))

Regulatory History and Device Description

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Regulatory History
Device Classification

- On market prior to Medical Device Amendments (May 28, 1976)
- Included in FDA's original device classification efforts
- Proposed rule (1978) – Neurological Devices Classification Panel:
  - » Identified risks: worsened psychological condition, electrical shock, and patient injury
  - » Cited: Butterfield (1975), Johnson (1970), Logan and Turnage (1975), and Thorne (1975)

Regulatory History
Device Classification

- Final Classification Rule:1979
- Class II – Premarket Notification (510(k))
- Regulation (21 CFR 882.5235):

"…an instrument used to administer an electrical shock or other noxious stimulus to a patient to modify undesirable behavioral characteristics."

510(k) Cleared Devices for the Treatment of SIB

- **Stimulator Sonic Control ("Whistle Stop")** - Farrall Instruments Inc. (K760166)
- **Self-Injurious Behavior Inhibiting System (SIBIS)*** - Oxford Medilog, Inc. (K853178)
- **SIBIS Remote Actuator -** Human Tech. Inc. (K871158)
- **Graduated Electronic Decelerator (GED)*** - Judge Rotenberg Center (JRC) (K911820)

* *Specifically indicated to be used only in patients where other forms of therapy have been attempted and failed.*

General Device Components

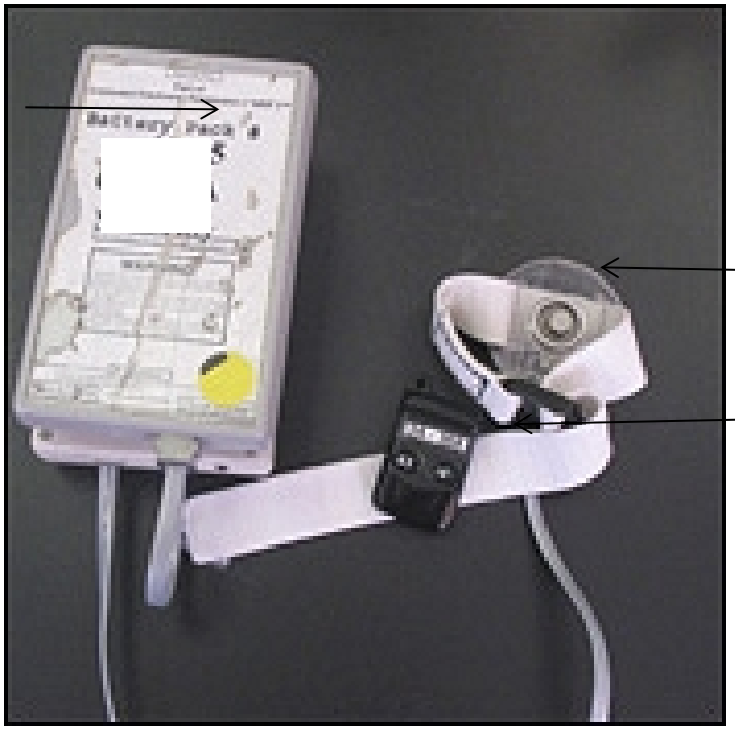

Figure 1: GED Electrical Stimulus Generation Module and Remote Monitor K911820

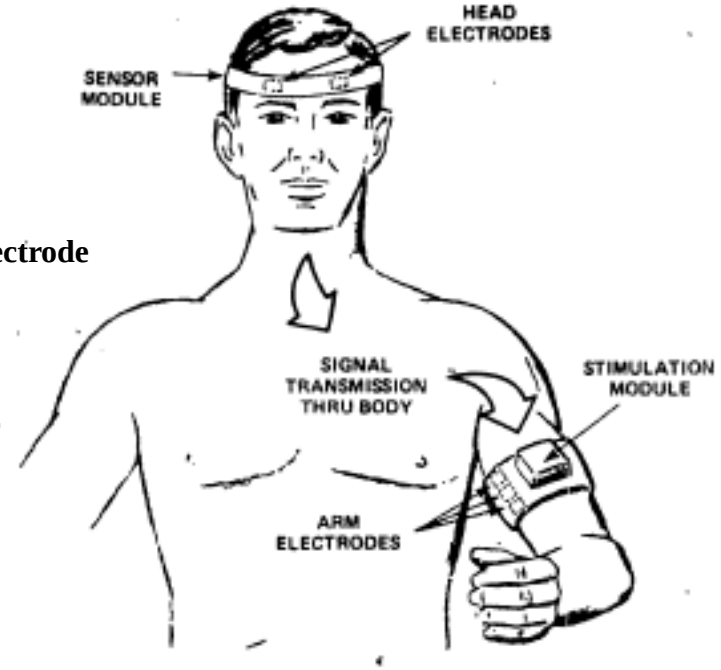

Figure 2: SIBIS System Cleared under K853178

510(k) Cleared Devices: Output Specifications

Device	Output Stimulus Parameters	Electrodes	Electrode Location(s) Per Instructions for Use
"Whistle Stop" (K760166)	Max Current: 10 mA @ 20 kΩ Max Voltage: 200V Frequency: 10 Hz Pulse Width: 1-2 ms Max Power Density: 0.02 W/cm^2 Biphasic Waveform Shock Duration: 0.5-12 s	Dual Button Electrodes	On one leg or one arm. About 1" apart.
SIBIS (K853178 and K871158)	Max Current: 10 mA (@ ? Ω Avg. (rms) Current: 3.5 mA @ 20kΩ Max Voltage, 200V Frequency: 20kHz signal modulated at 80 Hz Pulse Width: 6.2 ms Max Power Density: 0.16 W/cm^2 Biphasic Waveform Shock Duration: 0.1-0.2 s	Concentric ring Electrode Ring Surface Area (SA), 1.81 cm^2 Button SA, 0.19 cm^2	Uses a sensor module of the head to provide stimulation on the arms.

510(k) Cleared Devices: Output Specifications

Device	Output Stimulus Parameters	Electrodes	Electrode Location(s) Per Instructions for Use
GED/GED-1 (K911820)	Max Current: 29.4 mA @ 5 kΩ Avg (rms) Current: 12 mA @ 5 kΩ Max Voltage: 150 V Frequency: 80 Hz Pulse Width: 3.125 ms Max Avg Power Density: 1.01 W/cm^2 @ 5 kΩ Monophasic Waveform Shock Duration: 2 s	Concentric ring Ring SA, 0.7 cm^2 or Dual Button Electrodes (placed ≤ 6" apart) SA = 0.7 cm^2	Extremities (e.g., inner or outer surface of an arm or leg, the feet bottoms, palm, the upper three quarters-of the buttocks and the lower back, or the right side on the upper chest or back.

Modified Devices (Not FDA Approved/Cleared):

- GED-3A → similar output specification to GED
- GED-4 → an average output current that is almost three times that of the FDA cleared GED device (Israel et al., 2008)

Device Characteristics that Affect Stimulation Perception

- Current, Voltage, & Skin Resistance

  Ohm's Law: current = voltage/resistance
- Pulse Duration
- Shock Duration
- Stimulus Frequency and Waveform
- Electrodes (location and type)
- Repeated Shocks

Individual Patient Characteristics and Stimulation Perception

- Individual Patient Variability[1]
- Anxiety and Attention[2]
- Behavior Characteristics and Personality Traits[3]
- Autism Spectrum Disorder (ASD)[4]

1 Arntz and DeJong 1993; Blumenthal et al., 2001; Butterfield, 1975; Delitto et al, 1992; Duker et al., 1990; Jones et al., 1982; and Rollmann & Harris, 1987

2 Arntz and DeJong 1993 ; DeLitto, et al., 1992; Duker et al., 1999

3 DeLitto, et al., 1992; Duker et al., 1999

4 Allely, 2013

Clinical Background – Self Injurious Behavior (SIB) and Aggressive Behavior in Intellectual and Developmental Disorders

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Overview

- SIB/Aggressive Behavior in Persons with Intellectual/Developmental Disabilities
- Etiology of SIB/Aggressive Behavior
- Assessment of SIB/Aggressive Behavior
- Treatment of SIB/Aggressive Behavior
- Summary

SIB/Aggressive Behavior in Persons with Intellectual/Developmental Disabilities

- Relatively high prevalence of SIB/Aggressive Behavior in persons with autism spectrum disorders (ASDs), intellectual impairment, developmental disabilities and certain genetic disorders
- Estimates of SIB range from 2.6% - 40% (Griffin et al, 1987)
- 32% prevalence in clinic sample of children with developmental disabilities (MacLean et al, 2010)

SIB/Aggressive Behavior in Persons with Intellectual/Developmental Disabilities

- **Common SIBs:**
  - Head banging
  - Hand biting
  - Skin picking
  - Excessive scratching
  - Cutting

SIB/Aggressive Behavior in Persons with Intellectual/Developmental Disabilities

- **Serious SIBs**:
  - Eye gouging/poking with risk of blindness
  - Non-accidental injuries producing bleeding, protruding and broken bones
  - Swallowing dangerous substances or objects
  - Burning
  - Insertion of objects into body orifices
  - Genital mutilation
- **Aggressive Behavior** – conduct, due to intensity and/or frequency, that presents an imminent danger to the self or other persons and/or property

Etiology of SIB/Aggressive Behavior

- Etiology remains unclear
- Literature has suggested various biological and behavioral etiologies
- **Biological**:
  - **Biochemical** – release of beta endorphins, serotonergic dysfunction
  - **Seizures** – notably in frontal and temporal lobes
  - **Clinical features** of certain genetic disorders
  - **Hyper- and hypo-arousal levels**
  - **Pain** – response to pain (e.g., ear infection, migraine, G-I distress, etc.)
  - **Sensory** – abnormal (low) levels of physical stimulation

Etiology of SIB/Aggressive Behavior

- **Behavioral**: SIB/Aggressive Behavior learned via operant behavior principles and maintained by reinforcement
- **Behavioral**:
  - **Environmental hypothesis** - behavior shaped by various environmental contingencies (e.g., need to escape a stressful situation)
  - **Positive reinforcement hypothesis –** two broad classes:
    - Increased attention
    - Increased access to desirables

Etiology of SIB/Aggressive Behavior

- **Behavioral** (cont'd):
  - **Negative reinforcement hypothesis**
    - SIB/aggression used as escape or avoidance responses
    - Highest rates of SIB/aggression often displayed during the most difficult task conditions
  - **Self-stimulation hypothesis**
    - Behavior that occurs without observable environmental triggers
    - May be more common in institutionalized settings
    - May be linked to biological arousal hypothesis
  - **Communication hypothesis** – associated with difficulty in expressive and/or receptive language function

Assessment of SIB/Aggressive Behavior

- **Functional analysis** – identification of relationships between SIB/Aggressive Behavior and relevant antecedents and consequences
- **Descriptive analysis**
  - Direct observation via quantitative data collection (e.g., frequency counts, scatter plots, etc.)
  - Antecedent-behavior-consequence (ABC) observations
- **Behavioral rating scales**
  - Motivation Assessment Scale
  - Aberrant Behavior Checklist
  - Behavior Problems Inventory
  - Baby and Infant Screen for Children with Autism Traits

Treatment of SIB/Aggressive Behavior Literature Review

- **Pharmacological Treatments:**
  - Risperidone (2006) and aripiprazole (2009) only FDA-approved drugs to treat behaviors associated with autism
  - Other classes of drugs have been investigated
  - Studies limited by single case or small case series with different outcome measures
  - Cochrane review (2013): 5 randomized controlled trials in adults (4 opioid antagonist, 1 clomipramine)
  - Pharmacological treatments may reduce SIB/Aggressive Behavior if based upon a putative biological mechanism
  - AE profile similar to approved use patient populations
  - No higher risk of AE's in individuals with intellectual or development disabilities

Treatment of SIB/Aggressive Behavior Literature Review

- **Pharmacological Treatments:**
  - **Typical and atypical antipsychotics**
    - Risperidone most studied
    - Major effects on irritability and aggression with less reported efficacy for SIB
  - **Antidepressant agents**
    - SSRI's for stereotypic and obsessive-like behavior associated with SIB/Aggressive Behavior
    - Randomized trial of clomipramine demonstrated clinically significant improvement in the rate and intensity of SIB and stereotypy
  - **Opioid antagonists**
    - 4 randomized controlled trials of naltrexone vs. placebo with relatively modest reduction (~30%) in SIB/Aggressive Behavior
    - Effects largely short-term
    - May worsen SIB/Aggressive Behavior in the long-term, increasing relapse rates if discontinued

Treatment of SIB/Aggressive Behavior Literature Review

- **Pharmacological Treatments:**
  - **Mood stabilizers**
    - Lithium – utilized to augment SSRI's
    - Anticonvulsant agents – equivocal results
  - **Alpha agonists**
    - Used primarily to treat irritability
    - Clinical effect likely due to sedating effect of these drugs
  - **Others**
    - Amantadine – small randomized trial of autistic children with irritability and aggression
    - Ammonia – used as an aversive treatment with reported benefit in reducing SIB/Aggressive Behavior

Treatment of SIB/Aggressive Behavior Literature Review

- **Behavioral Approaches**:
  - Most common approach for treating SIB/Aggressive Behavior
  - Based upon concept that SIB/Aggressive Behavior is a learned behavior and responds to environmental modifications
  - Kahng et al (2002): quantitative analysis of behavioral treatment of SIB (1964-2000):
    - 396 articles, 706 participants
    - Mean outcome: 83.7% reduction in SIB from baseline to end of treatment
    - Reinforcement based treatments have increased; punishment-based interventions have decreased
    - Early and effective intervention essential to impact behavior change
    - Greater emphasis should be placed upon prevention

Treatment of SIB/Aggressive Behavior Literature Review

- **Behavioral Approaches:**
  - **Reinforcement-based treatments**
    - Positive
    - Negative
    - Noncontingent (NCR)
    - Different reinforcement of other behaviors (DRO)
    - Differential reinforcement of incompatible behaviors (DRI)
    - Differential reinforcement of low rates of behavior (DRL)
  - **Extinction-based treatments**
    - Discontinue reinforcement for a response that was previously reinforced
    - Use of protective equipment for severe SIB
    - “Extinction bursts” common during early phase of treatment

Treatment of SIB/Aggressive Behavior Literature Review

- **Behavioral Approaches:**
  - **Punishment-based treatments**
    - Use of aversive stimuli
    - Removal of a positive reward due to SIB/Aggressive Behavior
    - May be necessary for serious or dangerous SIB/Aggressive Behavior when other treatments have failed (Minshawi, 2008)
    - Stimuli or event must be strong enough to override the maintaining reinforcement for the behavior
  - **Functional Communication Training (FCT)**
    - Socially appropriate communicative behavior taught to replace less appropriate behavior
    - Allows the individual to regulate their reinforcement

Other Literature Reported Treatments of SIB/Aggressive Behavior

- **Physical restraint (non-punishment)**
  - Used to prevent injury to self or others via immobilization
  - Risk of injury and death if not properly supervised
- **Sensory Integration Training (SIT)**
  - Based upon theory that sensory dysfunction contributes to SIB/Aggressive Behavior
  - Goal of treatment is stimulation of neural networks involved in receiving, modulating, and integrating sensory input

Alternative Treatments of SIB/Aggressive Behavior

- **Mindfulness training** – meditation techniques
- **Contingent exercise** – brief physical exercise
- **Muscle relaxation**
- **Snoezelen room** – use a multi-modal sensory environment (e.g., olfactory, vibratory and tactile, visual, auditory)

Experimental Treatments of SIB/Aggressive Behavior

- **Surgical**
  - Ablative procedures – amygdalotomy, limbic leucotomy, cingulotomy, anterior capsulotomy
  - Deep brain stimulation – not FDA-approved for SIB/aggression; studies have targeted posterior hypothalamus
- **Electroconvulsive Therapy (ECT)**
  - Not FDA-approved for SIB/Aggressive Behavior
  - Case report of improvement in autistic boy with SIB/Aggressive Behavior and bipolar disorder

Defining Treatment Failure

- FDA cleared indication for ESDs for Aversive Conditioning (1986 & 1994):

  For the treatment of patients, usually diagnosed as retarded or autistic, who exhibit self-injurious behavior of sufficient intensity and frequency to cause serious damage to themselves. ***The device should be used only on patients where alternate forms of therapy have been attempted and failed.***

- Challenges for defining treatment failure:
  - Number of other, non-aversive treatments that must be tried first
  - Type of treatment (behavioral, pharmacological, alternatives, investigational)
  - Length of treatment (? weeks, months)
  - Lack of a definition of intolerance
  - Lack of “gold standard” objective criteria for determining response to therapy

Clinical Background Summary (I)

- SIB/Aggressive Behavior are common co-morbid behavioral conditions in individuals with intellectual and developmental disabilities
- Etiology of SIB/Aggressive Behavior in this population remains unclear and includes biological and behavioral theories
- Careful assessment of SIB/Aggressive Behavior assists in the targeting of appropriate treatment
- No current published consensus guidelines or practice parameters for the treatment of SIB/Aggressive Behavior
- Studies of safety and efficacy of treatment limited by lack of controlled trials and reliance on single case reports or small, open-label case series

Clinical Background Summary (II)

- Treatment of SIB/Aggressive Behavior consists primarily of behavioral and pharmacological interventions
  - Most treatments appear to be beneficial in reducing but not eliminating SIB/Aggressive Behavior
  - Literature suggests behavioral approaches should be the first line treatment
  - No specific behavioral treatment is the most effective
  - Pharmacological interventions may be more effective when combined with behavioral treatment

Clinical Background Summary (III)

- Reporting of adverse events limited to drug studies
- Adverse event profile of drugs similar to approved use patient populations
- No higher risk of AE's in individual with intellectual and development disabilities
- Adverse events can occur with some behavioral therapies, notably extinction treatment and punishment-based treatments
- Lack of data for defining treatment failure

Benefit Risk Assessment of ESDs for Aversive Conditioning

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FDA/CDRH/ODE/DNPMD

Sources of Information

- Systematic Literature Reviews for Benefits and Risks
- Manufacturer and User Facility Device Experience (MAUDE) Database
- Reviews and Reports from Independent Sources
- Prior Public Proceedings/Governmental Reports
- Information from Manufacturers
- Clinical Interviews Conducted by FDA
- Parental Reports/Case Reports from JRCPA Letter
- Other Sources

Methodology
Systematic Literature Review

- Separate searches for benefits and risks
- Databases: EMBASE, MEDLINE, PsycINFO
- Search strategy
- Results
  - » Benefits: 57 articles (45 clinical reports, 12 reviews)
  - » Risks: 39 articles (27 clinical reports, 12 reviews)

Benefits
Systematic Literature Review

- Total: 45 clinical reports identified
  - 1 case-control study conducted outside the U.S.
  - 1 within subjects comparison trial conducted outside the U.S.
  - 1 retrospective review of 60 patient charts conducted in the U.S.
  - 1 questionnaire follow-up study of 22 subjects (11 respondents) who had received ESD for aversive conditioning conducted in the U.S.
  - 41 case reports/case series
- No prospective randomized controlled trials

Case Control Study of ESD for SIB/Aggressive Behavior

Duker and Seys (2000)

- Prospective case control study: N=16 → 8 subjects with SIB compared with 8 matched controls
- Primary outcome measure: an author-defined mechanical restraint score
- Overall results: 82% of individuals receiving ESD benefited (over an 8 year period)
- Problems: adaptation, self-restraint, continued SIB
- Limitations
  - Primary outcome measure did not directly examine SIB
  - Unclear relationship between the mechanical restraint score and SIB
  - Small sample size

Within Subjects Comparison: Baseline vs. Device Applied

Duker and Van der Munckhof (2007)

- N=5
- Comparison of baseline heart rate vs. heart rate with ESD device applied
- Subjects wearing active ESD had significantly lower heart rate compared to baseline (not wearing device)
- Conclusion: Subjects less anxious with active device
- Limitations
  - Heart rate is not an accepted marker of anxiety state or SIB
  - Relationship between anxiety and SIB is not known
  - Small sample size

Retrospective Review of Patient Charts
Israel et al. (2008)

- N=60
- Devices: GED-1 (cleared), GED-4 (not cleared)
- ESD use as a supplement to positive programming led to ≥ 90% reduction in SIB/Aggressive Behavior in 100% of patients
- Limitations:
  - Retrospective review of clinical charts
  - Methodological considerations
  - Journal status unclear
  - Authors did not report conflict of interest

Questionnaire Follow-Up Study of ESD for SIB
Murphy and Wilson (1980)

- Follow-up study of 11 subjects who had received ESD for aversive conditioning
- Relapse defined as a “marked increase in self-injurious behavioral after treatment ended”
- 7 of 11 successfully treated patients relapsed within two years after treatment ended
- 2 showed continued suppression of SIB symptoms
- Limitations:
  - » Questionnaire assessment
  - » No statistical analysis
  - » Small sample size

Case Reports/Series of ESD Use for SIB/Aggressive Behavior

- 41 Articles (N=105 individual reports)
- Short-Term Benefit (while device is applied)
  - » 66 had immediate reduction in SIB/Aggressive Behavior
  - » 10 had partial reduction in SIB/Aggressive Behavior
  - » 3 reported no benefit
- Long-Term Benefit
  - » Continued device application
    - 23 had continued reduction in SIB/Aggressive Behavior
    - 6 lost initial reduction in SIB/Aggressive Behavior
    - 2 equivocal results
  - » With device use tapered off (fading)
    - 3 had continued reduction in SIB/Aggressive Behavior after device removed
    - 3 lost initial reduction in SIB/Aggressive Behavior
- Limitations: Different devices, device use, stimulation parameters, duration, endpoint assessment, concurrent treatments

Magnitude and Duration of Effect May Be Dose-Dependent

- Initial reduction in SIB/Aggressive Behavior and overall duration of reduction may be related to ESD stimulus intensity (Williams, Kirkpatrick-Sanchez, and Iwata, 1993)
- Loss of reduction of SIB in previous reports may be due to lower level stimulation (Duker and Seys, 2000)

Benefits

Summary of Published Review Articles

- General support for short-term reduction in SIB/Aggressive Behavior
- Long term durability of effect in question
- Comparison of different treatments
  - Punishment quickest to suppress behavior, but least durable
  - Long-term benefits: time-out, differential reinforcement best outcomes

Benefits

Summary of Published Review Articles

- **Conclusions**
  - Short-term reduction of SIB/Aggressive Behavior with ESD use may be supported
  - Long-term benefits less well-established, with possibility of relapse
  - Magnitude and duration of effect may be dose dependent
- **Limitations**
  - Lack of prospective, randomized or placebo controlled or comparative trials
  - Different devices and device administration
  - Non-systematic assessment, no statistical analyses
  - Non-adherence to modern research/publication standards

Risks
Systematic Literature Review

- Total: 27 articles identified
  - 1 prospective case-control trial
  - 1 retrospective review of 60 patient charts
  - 25 case reports/series (N=66)

- 16 other case report/series did not mention assessing AEs or the occurrence of AEs

Case Control Study/Retrospective Review

- **Case Control Study** (Duker and Seys, 2000; N=16)
  - No systematic report of AEs by subject
- **Retrospective review of 60 patient charts** (Israel et al., 2008)
  - One negative side effect: skin discoloration
  - Some reactions, including emotional reactions, not considered AEs

Case Reports/Series
Patient AE Reports Associated with ESD for Aversive Conditioning for SIB/Aggressive Behavior

- Total: 27 articles, N=66 individual reports
- AE Reports
  - Anxiety (6 reports)
  - Fear and aversion/avoidance (6 reports)
  - Substitution of other negative behaviors (5 reports)
  - Burns and other tissue damage (4 reports)
  - Depression/crying (4 reports)
  - Pain/discomfort (3 reports)
  - Neurological symptoms (1 report)
  - Other negative emotional reactions or behaviors (11 reports)

Other Articles

Patient AE Reports Associated with ESDs for Aversive Conditioning for Other Indications

- 3 (of 15) Articles Reported AEs
- AE Reports
  - Anxiety
  - Psychotic delusions
  - Headaches
  - Restlessness
  - Mild dysphoria
  - Mild transient depression

Risks
Summary of Published Review Articles

- Most acknowledge the possibility of negative emotional reactions
- Negative emotional reactions
  - Fear, avoidance, aversion, anxiety and depression
- Other possible adverse events
  - Retaliation, increased aggression, or substitution of one injurious behavior for another
- Two reviews concluded that ESDs for aversive conditioning are not associated with any significant adverse events

  (Carr and Lovaas, 1981; Bachman, 1973)
- One review contends that physical discomfort and emotional reactions are required in order for the treatment to be effective

  (Lichstein and Schreibman, 1976)

Risks

Summary of Systematic Literature Review

- **Potential Risks**:
  - Pain
  - Physical injury (burns, tissue damage, neurological symptoms)
  - Psychological AEs (anxiety, fear, aversion/avoidance, depression, other)
- **Limitations:**
  - No systematic investigation of AEs reported or described
  - Subject population may have difficulty reporting AEs
  - Evolving conceptions of disease and pathophysiology

Other Sources of Information

- MAUDE Database
- Reviews and Reports from Independent Sources
- Prior Public Proceedings/Governmental Reports
- Information from Manufacturers
- Clinical Interviews Conducted by FDA
- Parental Reports/Case Reports from JRC Parents Association
- Other Sources

MAUDE Database

1 AE report (1995)

Inadvertent deployment of an ESD for aversive conditioning (a “GED device”) with resulting skin lesions, including “2 ring-shaped marks” and 3 areas of “rough skin”.

Scientific Organization Position Statements

- AMA Council on Scientific Affairs (1987)
  - "…when behavior is dangerous and has not improved with less intrusive procedures, increasingly aversive techniques, up to electric shock for the most severe, are appropriate."
- NIH Consensus Development Conference (1989)
  - Behavior reduction interventions appeared to be effective in some individuals, particularly in suppressing SIB
  - Anecdotal reports of negative side effects of behavioral enhancement and behavior reduction approaches
  - Behavior reduction interventions may be selected for their rapid effects
  - Should be used as part of a comprehensive treatment package

NYSED Report (2006) and Massachusetts DDS Findings (2011)

- **NYSED**: Concluded use of all aversive interventions are associated with substantial risk, and ESD use at JRC raises health and safety concerns
  - Skin burns
  - Psychological side effects (fear, aggression, anxiety, depression, suicidality, anxiety, PTSD, social withdrawal)
- **Mass. DDS**: In 2011, prospectively prohibited Level III behavioral interventions (including ESDs for aversive conditioning)
  - "current standard of care for individuals with intellectual disability with the most severe behavioral challenges is positive behavior intervention and does not include aversive interventions or punishment"

Massachusetts Disabled Persons Protection Committee Complaints (1993-2013)

- Burns/tissue injury – 6 reports
- Inappropriate device use – 3 reports
- Negative emotional reactions – 3 reports
- PTSD - 1 report

National Disability Organizations
(2010-2013)

- **National Disability Organizations**
  - National Council on Disability (NCD), Disability Rights International (DRI), National Disability Rights Network (NDRN), the Arc, and National Leadership Consortium on Developmental Disabilities (NLCDD)
- **Information**
  - ESDs for Aversive Conditioning are banned in most states
  - Adverse events: 4 cases of psychological trauma and PTSD symptoms
  - Alternative treatments (positive environmental and reinforcement strategies) are currently effective for severe and refractory self-injury
  - ESD use is “inherently unsafe”

MDRI Report and UN Response

- MDRI (2010)
  - Report of AEs
    - Level of pain experienced is significant
    - Occurrence of tremor, burns and tissue injury
    - Fear, and other negative emotional and behavioral reactions
    - Potential risk of psychological trauma, marginalization, or alienation
- UN Special Rapporteur on Torture or other Cruel, Inhuman or Degrading Treatment or Punishment
  - Letter (2012) to US Dept. of State with concerns about the harms suffered by residents of the JRC
  - Follow up investigation (2012) resulted in call for absolute ban on “all coercive and non-consensual measures, including “electroshock” procedures used at JRC

Manufacturer Information Obtained by FDA Office of Compliance (2011-2013)

- Patient Case Summaries (2013)
  - All demonstrated significant reduction in SIB/Aggressive Behavior with ESD use
  - No adverse events reported
- GED Files (2009-2011)
  - 1 burn reported
- Parent report of benefit to his child with ESD at JRC (Meeting with JRC in 2013)
- "JRC Policy" Document (2012)
  - Increases in aggression, escape behaviors, emotional reactions, sleep difficulties
  - Other physical or emotional reaction or change…not only immediate, physical observations (such as temporary redness of the skin), but also longer-term, non-physical consequences

Clinical Interviews (2014)

Interview	Benefits	Reported AEs
1	ESD not effective	Burns, fear, generalized anxiety, panic when reminded of shocks, flashbacks
2	Device worked when applied but lost effect when patient was taken off	- Multiple burns on skin, but no permanent marks or scars; anxiety - No long-term effects, PTSD symptoms, or depression
3	Decreased SIB behaviors, but did not address underlying condition	Anxiety, aggression toward staff, burns, scars, paresthesia/loss of sensation/numbness, muscle spasm, heart palpitations, seizure, fear, depression, suicidality, nightmares, flashbacks, re-experiencing

Parent Reports (2013)

- Letter from JRCPA, with 3 letters from parents attached and 7 case reports
- ESDs described as the only successful treatment option for certain individuals
  - Significant decrease in SIB with device administration
  - For the first time in their lives, patients can “be happy”
- Parents contend that premature termination of use of the device will cause great harm

Other Reports (2006-2014)

- Media Reports
  - Newspaper, magazine and TV reports
  - Claims of device misuse, pain, burns, depression, suicidality, PTSD
  - At least 3 reports supportive of ESD use

Limitations of Sources of Information

- Literature Review
  - Relative lack of systematic investigation
  - Potential bias
- MAUDE Database: only 1 report
- Professional/Scientific Organizations
  - Not specific to ESDs for aversive conditioning
  - Conducted over 25 years ago
- Independent/Governmental Reports
  - Conducted in response to certain circumstances
- Manufacturers and Advocacy Organizations
  - Represent a particular perspective
- Interviews and Parental reports: selection bias
- Other sources: no systematic assessment, agenda

Benefits
Summary of Available Information

- Short-term (when the device is applied) reduction of SIB/Aggressive Behavior with ESD use may be supported
- Long-term benefits less well-established, with possibility of relapse with device withdrawal

Risks

Summary of Available Information

Potential AEs (greatest to least number of reports):

- Other negative emotional reactions or behaviors
- Burns and other tissue damage
- Anxiety
- Acute stress/PTSD
- Fear and aversion/avoidance
- Pain/discomfort
- Depression (and suicidality)
- Substitution of other negative behaviors (including aggression)
- Psychosis
- Neurological symptoms and injury

Ethical Considerations in the Use of Aversive Conditioning ESDs

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U.S. Food and Drug Administration, Silver Spring MD

CDRH Panel Meeting, April 24, 2014

Introduction

- Additional data from clinical investigations would better inform the risk assessment
- FDA has identified serious concerns regarding the protection of the rights, safety, and welfare of any subjects in clinical investigations in which ESDs are used on human subjects, and the permissibility of such studies under FDA regulations for both children and adults
- These concerns exist irrespective of whether the device is banned

Topics

- Additional Safeguards for Children in Clinical Investigations
- Applying the Additional Safeguards to the Use of Aversive Conditioning ESDs in Clinical Investigations Involving Children
- Risks and Benefits of ESDs in the Clinical Setting
- Risks and Benefits of ESDs in Adult Subjects

Additional Protections for Children

21 CFR 50 subpart D

- Clinical investigations involving children
  - » must be restricted to either “minimal” or a “minor increase over minimal” risk absent a potential for direct benefit to the child, or
    - *21 CFR 50.51/53*
  - » must offer a prospect of direct benefit; and present risks that are justified by anticipated direct benefits to the child, the balance of which is at least as favorable as any available alternatives, or
    - *21 CFR 50.52*
  - » must be reviewed by a federal panel, with a final determination on the acceptability of the protocol by the FDA Commissioner
    - *21 CFR 50.54*

Applying the Additional Safeguards

- Known risks of ESDs exceed “minimal” and a “minor increase over minimal” risk, and hence ESD use cannot be approved under 21 CFR 50.51 or 50.53
- Research use of aversive conditioning ESDs evaluated under 21 CFR 50.52:
  - » Clinical investigations presenting the prospect of direct benefit to individual subjects may involve children if:
    1. The risk is justified by the anticipated benefit to the subjects;
    2. The relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches;

Available Alternatives?

- Criterion: “relation of the anticipated benefit to the risk is at least as favorable…as that presented by available alternative approaches”
  1. Least restrictive intervention that controls the self-injurious behavior should be used
  2. ESDs are a highly restrictive intervention
  3. Thus, use of ESDs must be limited to persons who are refractory to or unable to tolerate adequate treatment attempts with all other less restrictive interventions administered by appropriately qualified clinicians

Risks and Potential Benefits in a Refractory Population?

- Criterion: “risk is justified by the anticipated benefit to the subjects”
  - » Even if a refractory patient population can be identified, there must still be a sufficient prospect of direct benefit to justify the risks of using aversive conditioning ESDs
  - » FDA review identified case reports and case series suggesting a short term reduction in self-injurious behaviors with ESD use, but raised concerns due to the lack of data on long-term effects, and the numerous potential serious risks identified

Concerns Regarding Risks and Benefits

- The harms associated with the use of aversive conditioning ESDs may not be justified by the potential benefits, even in populations that are considered “refractory.”
- Thus, the investigational use of these devices may not be permissible under 21 CFR 50.52.
- Due to similar considerations regarding risks, benefits, and alternatives in the clinical setting, the Agency questions whether clinical use of aversive conditioning ESDs is justified, even in populations that may be considered “refractory.”

ESD Use in Adults

- FDA regulations at 21 CFR 56.111 require that the risks of the study are minimized, the risks are reasonable in relation to anticipated benefits and knowledge that may be expected to result from the study, and that selection of subjects for the study must be equitable.
- FDA concerned that risks to subjects are not minimized, and the rights, safety, and welfare (particularly of subjects with developmental disabilities) may not be adequately protected if a less restrictive therapy exists with a more favorable risk/benefit profile.

Ethical Considerations Summary

- The Agency is concerned that the research use of aversive conditioning ESDs in children may not be permissible under 21 CFR 50 subpart D.
- The Agency is concerned that the potential benefits of using aversive conditioning ESDs in children may not outweigh the risks in the clinical setting.
- The Agency is concerned that the risks to adult subjects may not be appropriately minimized, and the rights, safety, and welfare of subjects with developmental disabilities may not be adequately protected.

FDA Summary

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FDA Summary (I)

FDA is convening this Advisory Panel meeting to seek scientific and clinical expert opinion on the risks and benefits of ESDs for aversive conditioning and to obtain recommendations that will assist the Agency in considering whether or not to ban these devices.

FDA Summary (II)

When determining whether there is a *substantial and unreasonable risk of illness or injury* the Panel should weigh each of the following (taking into consideration the lack of high quality data):

- The potential risks and benefits of ESD use
- The potential risks and benefits of alternative treatments
- The potential risks of leaving patients untreated or inadequately treated (which may include a greater risk of morbidity or mortality) by the use of potentially ineffective therapy

FDA Summary (III)

FDA will be asking the Panel to provide feedback on the following:

- Risks and benefits associated with other treatment options for this population. (Panel Question 1)
- Risks and benefits of ESDs for aversive conditioning to modify undesirable behavioral characteristics in patients who exhibit SIB and aggressive behavior. (Panel Questions 2)
- Whether ESDs for aversive conditioning present a substantial and unreasonable risk of illness or injury. (Panel Question 3)
- Potential approaches to risk mitigation. (Panel Question 4)

FDA Summary (IV)

- The risks and benefits of applying the ban to devices currently in use by patients. (Panel Question 5)
- Whether a clinical trial could be conducted to evaluate ESDs for aversive conditioning for the treatment of SIB and aggressive behavior. (Panel Question 6)

Panel Questions

Background

FDA is considering issuing a proposal to ban aversive conditioning electrical stimulation devices (ESDs) that are intended to administer a noxious electrical stimulus to modify undesirable behavioral characteristics in patients who exhibit self-injurious behavior (SIB) and aggressive behavior. Section 516 of the FD&C Act (21 U.S.C. § 360f) authorizes FDA to ban a medical device that presents "*an unreasonable and substantial risk of illness or injury*" based on all available data and information.

Question 1

In assessing the reasonableness of the risk of illness or injury posed by a device, FDA considers the availability of other treatment options, including pharmacological, behavioral, alternative, and experimental therapies for the treatment of SIB and aggressive behavior.

a. In general, do you think these other treatments are adequate to address SIB and aggressive behavior?

b. Is there is a specific subpopulation of patients exhibiting SIB and aggressive behavior for which these options are inadequate?

Question 2a

When determining whether the risk of illness or injury posed by a device is "substantial," FDA will consider whether the risk is important, material, or significant in relation to the device's benefit.

a. Please discuss whether the available evidence presented at this Panel meeting demonstrates that ESDs that are intended to administer a noxious electrical stimulus for the modification of SIB and aggressive behavior provide a benefit. If so, please identify any specific population(s) of patients for which benefit has been demonstrated.

Question 2b

b. FDA has identified the following potential risks related to the use of ESDs that are intended to administer a noxious electrical stimulus for the treatment of SIB and aggressive behavior: other negative emotional reactions or behaviors, burns and other tissue damage, anxiety, acute stress/PTSD, fear and aversion/avoidance, pain/discomfort, depression (and possible suicidality), substitution of other negative behaviors (including aggression), psychosis, and neurological symptoms and injury. Please comment on whether this represents a complete list of risks, whether there any additional risks that you think should be included, and whether any of the risks listed above are not risks posed by ESDs.

Question 3

Section 516 of the FD&C Act (21 U.S.C. § 360f) sets forth the standard for banning devices. Under that provision, FDA is authorized to ban a device if the device presents *"an unreasonable and substantial risk of illness or injury*" based on all available data and information. Considering the adequacy and availability of alternatives to treat patients exhibiting SIB and aggressive behavior, as well as the benefits ESDs may provide for these patients, please discuss whether ESDs intended to administer a noxious electrical stimulus for the treatment of SIB and aggressive behavior present a substantial and unreasonable risk of illness or injury. In your response please explain your reasoning.

Question 4

If FDA determines that a device does present an unreasonable and substantial risk of illness or injury, the Agency next considers whether this risk may be corrected or eliminated by labeling, and may also consider whether imposing other requirements could correct or eliminate this risk. Please identify potential risk mitigations, and discuss how they would address the identified risks.

Question 4 (cont.)

Examples of potential risk mitigation include but are not limited to:

- Restriction on device technology and use (e.g., electrical stimulation output parameters, limitations of number and/or locations of electrode permitted on an individual).

- Labeling restrictions (e.g., indication only for use in treating only certain populations (e.g., treatment refractory patient populations, patients in certain age groups) or indication for use only when significant (e.g., life-threatening) self-injurious and/or assaultive/aggressive behaviors are being exhibited).

Question 5

If FDA determines that a device presents a substantial and unreasonable risk of illness or injury and proposes to ban it, the Agency must specify whether the ban applies only prospectively or also applies to devices in distribution and/or in use by patients. Please discuss the risks and benefits of applying the ban to devices currently in use by patients, and any recommendations regarding how patients should be transitioned to alternative treatments.

Question 6

Should the FDA determine not to ban these devices, the Agency may need to determine whether a clinical study could be conducted. Therefore, please discuss what concerns, if any, you may have about conducting a clinical study with these devices in either children or adults.